**Integrative Management of Chronic Cough Associated with Gastroesophageal Reflux Disease: Physiological and Psychogenic Perspectives**

**ABSTRACT**

**Aims:** This study investigates the association between gastroesophageal reflux disease (GERD) and chronic cough with psychogenic components, identifying both physiological and psychological mechanisms that contribute to symptom persistence. It also evaluates therapeutic strategies including pharmacological treatments, such as proton pump inhibitors (PPIs), baclofen, and neuromodulators, alongside behavioral interventions like cognitive-behavioral therapy (CBT).

**Study Design:** Integrative literature review.

**Place and Duration of Study:** Databases searched (PubMed, SciELO, BVS, LILACS, Medline) between March and June 2025.

**Methodology:** This study followed PRISMA guidelines for integrative reviews. Searches were performed using descriptors including "Cough," "Gastroesophageal Reflux," "Psychogenic," and "Therapeutics." Studies were included if published between 2014 and 2024, freely available in full text, and methodologically robust (randomized controlled trials, systematic reviews, or well-defined observational studies). After applying eligibility criteria and qualitative analysis, 17 studies were selected for inclusion.

**Results:** GERD-related chronic cough was found to involve both vagal-mediated reflexes and microaspiration, with esophageal hypersensitivity as a contributing factor. Psychogenic influences—such as anxiety, stress, and sensory hypervigilance—amplified symptom perception and limited response to acid suppression alone. PPIs showed modest effectiveness, particularly in non-acid or functional reflux cases. Adjunct therapies including baclofen, gabapentin, and CBT demonstrated improved symptom control, while Nissen fundoplication surgery was effective in selected refractory cases. Integrative treatment combining medical, surgical, and psychological approaches yielded the best outcomes.

**Conclusion:** Chronic cough associated with GERD is a multifactorial condition requiring individualized, multidisciplinary treatment. Optimal management involves not only acid reflux control but also the inclusion of behavioral and neuromodulatory strategies. Future studies should further investigate these integrated therapeutic pathways.

Keywords: stroesophageal Reflux Disease, Chronic Cough, therapeutic pathways

1. **INTRODUCTION**

Chronic cough, defined as a symptom persisting for more than eight weeks, is a frequent concern in respiratory care and is significantly associated with reduced quality of life. Among its most common causes, Gastroesophageal Reflux Disease (GERD) stands out, particularly due to its extraesophageal manifestations such as laryngitis, hoarseness, and refractory cough [1,2].

The connection between GERD and chronic cough is supported by multiple pathophysiological mechanisms. Two primary pathways have been proposed: (i) the vagal esophageal reflex, in which gastric reflux activates acid-sensitive receptors in the esophagus, triggering afferent vagal pathways that elicit cough; and (ii) microaspiration of gastric contents, which directly irritates and sensitizes the upper and lower airways [3–5]. These processes not only provoke coughing episodes but also contribute to cough reflex hypersensitivity, reinforcing a cycle of persistent symptoms.

However, current understanding extends beyond purely physiological factors. Psychosocial components, including anxiety, sensory hypervigilance, and somatoform traits, play a significant role in the persistence and amplification of symptoms in GERD-related cough. Research indicates that heightened symptom perception and maladaptive behavioral responses may sustain cough even in the absence of ongoing acid exposure [5–8]. This underscores the importance of recognizing a psychogenic dimension in many cases.

From a therapeutic perspective, proton pump inhibitors (PPIs) remain the first-line treatment aimed at suppressing gastric acid secretion. Nevertheless, many patients experience incomplete or absent symptom relief, particularly in the presence of non-acid reflux, esophageal hypersensitivity, or coexisting psychiatric conditions [8–10]. In such scenarios, alternative strategies are increasingly emphasized. Neuromodulators such as baclofen, a GABA-B receptor agonist that reduces transient lower esophageal sphincter relaxations, have shown clinical benefit [7–9]. Moreover, behavioral interventions, especially Cognitive Behavioral Therapy (CBT), have demonstrated effectiveness in addressing symptom-related anxiety and hypervigilance, leading to substantial improvements in cough frequency and patient well-being [10–12].

Given the multifactorial etiology of GERD-associated chronic cough, clinical management must adopt a personalized and multidisciplinary approach, integrating physiological, neurological, and psychological domains. This review therefore aims to provide an integrative overview of the underlying physiological and psychogenic mechanisms, as well as current and emerging treatment modalities, in order to inform more effective and individualized clinical practice.

**MATERIAL AND METHODS**

This integrative review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with the objective of identifying, evaluating, and synthesizing recent evidence on the relationship between Gastroesophageal Reflux Disease (GERD), chronic cough, and psychogenic or neurogenic factors, as well as related therapeutic strategies.

The literature search was conducted between March and June 2025 using the PubMed, SciELO, LILACS, BVS, and Medline databases. Controlled descriptors (MeSH/DeCS) and free-text terms were used in Portuguese, English, and Spanish, combined using Boolean operators (AND/OR). The search strategy included: (“cough” OR “chronic cough”) AND (“gastroesophageal reflux” OR “GERD”) AND (“psychogenic” OR “anxiety” OR “sensory hypersensitivity”) AND (“treatment” OR “therapy” OR “intervention”).

Inclusion criteria comprised studies published from 2014 to 2024, available in full text with free access, and written in Portuguese, English, or Spanish. Eligible study types included randomized controlled trials, systematic reviews, meta-analyses, observational studies, and narrative reviews with clearly defined methods. Case reports, editorials, letters to the editor, duplicates, and articles that did not directly address the association between GERD and chronic cough were excluded.

The selection process occurred in three phases. Initially, two independent reviewers screened titles and abstracts. In the second phase, the full texts of potentially relevant articles were assessed. Lastly, eligibility criteria were applied, and disagreements between reviewers were resolved by a third evaluator.

Data extraction covered author, publication year, study type, population, objectives, interventions, and key outcomes. The synthesis was qualitative and thematically organized into three categories: pathophysiological mechanisms, psychogenic factors, and therapeutic approaches. At the end of the selection process, 17 articles met all criteria and were included in this review.

1. **RESULTS AND DISCUSSION**

Seventeen studies published between 2014 and 2024 were analyzed to investigate the intricate relationship between gastroesophageal reflux disease (GERD), chronic cough, and psychogenic or neurogenic mechanisms. Findings were categorized into three interrelated domains—pathophysiological mechanisms, psychological influences, and therapeutic approaches—highlighting the multifactorial nature of GERD-related cough and the need for integrated management strategies.

GERD has been consistently associated with chronic cough through two primary mechanisms: the esophagotracheal reflex and direct microaspiration. In the first mechanism, reflux of gastric contents into the distal esophagus stimulates vagal afferent fibers via chemoreceptors and mechanoreceptors, triggering a centrally mediated cough reflex even in the absence of visible aspiration. This vagally mediated esophagotracheal reflex underscores the role of neural pathways in cough induction, independent of physical irritation in the airway [12–17]. The second mechanism involves microaspiration of gastric contents into the upper respiratory tract, leading to direct mucosal injury, chronic inflammation, and progressive sensitization of cough receptors in the larynx and trachea. This process can establish a cycle of peripheral neuroinflammation that perpetuates the cough reflex over time [15–21].

Additionally, esophageal hypersensitivity and motility disorders, such as ineffective esophageal motility and hypotensive lower esophageal sphincter tone, have been frequently identified in chronic cough cases, particularly where non-acid reflux is present. In such patients, conventional pH monitoring may fail to detect reflux episodes, requiring impedance-pH studies to identify non-acid events contributing to symptom persistence [5,6,9,16].

Psychogenic and central neurogenic factors significantly influence the persistence of cough, especially when reflux has been successfully managed pharmacologically. Studies indicate that anxiety, central sensitization, and cough hypersensitivity syndrome are commonly observed in patients with refractory symptoms [21–23]. These individuals often exhibit heightened responsiveness to sensory stimuli, with even minor esophageal or laryngeal irritation producing exaggerated cough responses. Neuroplastic changes in central processing areas involved in cough modulation—such as the nucleus tractus solitarius and periaqueductal gray—are thought to contribute to this sensitization, explaining why some patients fail to respond to acid-suppression therapy [8,9,24].

Proton pump inhibitors (PPIs) remain the frontline pharmacological therapy for GERD-associated chronic cough, aimed at reducing gastric acid exposure and preventing reflux episodes. However, clinical trials and observational studies have shown that their effectiveness is limited in patients with non-acid reflux, esophageal hypersensitivity, or psychological comorbidities, with success rates often falling below 50% [25–28]. In these refractory cases, neuromodulatory agents have emerged as viable alternatives. Baclofen, a GABA-B receptor agonist, has shown moderate effectiveness by reducing transient lower esophageal sphincter relaxations, thus lowering the frequency of reflux events [6,11,19]. Gabapentin, primarily used for neuropathic pain, appears to reduce central cough reflex sensitivity, leading to symptomatic improvement in patients with neurogenic or idiopathic cough [19].

Beyond pharmacological approaches, behavioral and procedural interventions have demonstrated growing relevance. Cognitive-behavioral therapy (CBT) targets maladaptive thought patterns, health anxiety, and hypervigilance, which often exacerbate the perception of cough. Several studies support the use of CBT and related behavioral interventions in improving symptom control and quality of life in patients with chronic, idiopathic, or neurogenic cough [9,10,16,17,19]. Laryngeal desensitization techniques, including voluntary cough suppression and vocal hygiene education, have also proven effective in reducing cough frequency and improving functional voice outcomes. In select patients with pronounced laryngeal hypersensitivity, superior laryngeal nerve blocks have been employed to disrupt afferent signaling and achieve symptom relief [16,17,19].

For patients with objective evidence of pathological reflux who have not responded to pharmacologic or behavioral therapy, surgical intervention remains a valuable option. Nissen fundoplication, which reinforces the lower esophageal sphincter, has been associated with symptomatic resolution in 70–85% of well-selected cases [4,17,22]. These results suggest that in anatomically driven or mechanically severe reflux, surgical correction can effectively eliminate the underlying stimulus for chronic cough.

Interestingly, complementary and herbal medicine has also entered the therapeutic landscape. Trials evaluating combinations such as Ojeok-San and Saengmaek-San have shown reductions in both cough severity and gastrointestinal symptoms, suggesting potential anti-inflammatory and esophageal-protective effects, although further studies are required to confirm these findings [19].

In summary, chronic cough associated with GERD reflects a complex interplay of gastroesophageal, neurogenic, and psychogenic mechanisms. Effective management must go beyond acid suppression to include central desensitization strategies, behavioral modification, and, when indicated, surgical or complementary approaches. This integrative perspective enables a more tailored and multidisciplinary response to a symptom that significantly impairs patient quality of life and often resists conventional treatment.

Table 1. Mechanisms linking GERD to chronic cough

| Mechanism | Description |
| --- | --- |
| Vagal esophagotracheal reflex | Acid stimulates vagal afferents triggering cough reflex |
| Microaspiration | Gastric contents inflame upper airway, activating cough receptors |
| Esophageal hypersensitivity | Heightened perception to normal esophageal stimuli |
| Motility dysfunction | Lower esophageal sphincter impairment permits non-acid reflux |

Table 2. Therapeutic interventions and outcomes

| Therapy | Primary Indication | Reported Effectiveness |
| --- | --- | --- |
| PPIs | Documented acid reflux | ~52% symptom improvement |
| Baclofen / Gabapentin | Non-acid reflux, neurogenic cough | Moderate symptom reduction |
| CBT and desensitization therapies | Idiopathic/psychogenic cough | Reduced frequency and distress |
| Fundoplication surgery | Confirmed reflux, failed pharmacological therapy | 70–85% complete symptom remission |
| OJS + SMS herbal combination | Functional GI and cough symptoms | Significant improvement in RCT |

1. **DISCUSSION**

This integrative review reaffirms the complex and multifactorial etiology of chronic cough associated with gastroesophageal reflux disease (GERD), highlighting the intricate convergence of peripheral physiological mechanisms, central nervous system sensitization, and psychological comorbidities in the persistence of symptoms. Although acid reflux and microaspiration have historically been regarded as the principal drivers of cough pathogenesis, a growing body of evidence indicates that these mechanisms alone are insufficient to explain the chronicity of symptoms in a substantial proportion of patients. Indeed, numerous studies report that even after achieving effective acid suppression with proton pump inhibitors (PPIs), a significant subset of patients continues to experience debilitating cough [1,5,11].

One of the most compelling explanations for this paradox lies in the role of the vagal esophagotracheal reflex, which represents a non-aspiration-dependent neural mechanism through which non-acid refluxate can provoke coughing. This reflex is mediated by vagal afferent fibers innervating the distal esophagus that transmit nociceptive signals to the nucleus tractus solitarius in the medulla, triggering the cough motor response. Notably, this reflex can be initiated by mechanical distension or exposure to weakly acidic or even non-acidic reflux contents, which may not be detected by conventional pH monitoring, thereby explaining the therapeutic failure of acid suppression alone [3,14,25].

Compounding this mechanism is the phenomenon of esophageal hypersensitivity, in which the esophageal mucosa becomes pathologically responsive to otherwise innocuous stimuli. This condition is frequently observed in patients with functional or non-erosive reflux and may reflect alterations in peripheral sensory receptors (e.g., TRPV1, ASIC3) or central amplification of sensory input. Moreover, the presence of transient lower esophageal sphincter relaxations (TLESRs), which allow for reflux in the absence of sphincter hypotonia, has been implicated as a key driver of recurrent reflux episodes in this population [6,14,17,26]. Together, these findings underscore the neurogenic basis of chronic cough in GERD, shifting the therapeutic paradigm beyond acid-centric models.

Pharmacological interventions targeting these neural pathways—specifically baclofen and gabapentin—have demonstrated modest but consistent therapeutic benefits. Baclofen acts as a GABA-B receptor agonist, reducing the frequency of TLESRs and thereby decreasing reflux events regardless of their pH characteristics. Gabapentin, conversely, modulates central sensitization by attenuating neuronal excitability within the brainstem cough centers, potentially reversing the neuroplastic changes underlying cough hypersensitivity [6,11,17,25]. While neither agent offers a universal solution, their success in refractory populations supports a shift toward neuromodulation-based therapy in selected cases.

Equally pivotal to symptom perpetuation are psychological and psychosomatic factors, particularly anxiety, chronic stress, and somatic hypervigilance. These elements contribute not only to the subjective amplification of symptom perception but also to actual alterations in central neural processing, a phenomenon described as central neuroplasticity [7,8]. Chronic exposure to visceral discomfort and respiratory irritation may sensitize central neural circuits—specifically the insula, anterior cingulate cortex, and prefrontal cortex—which are involved in interoception and affective modulation. As a result, patients may develop cough hypersensitivity syndrome (CHS), characterized by abnormal laryngeal sensations, heightened response to low-threshold stimuli (hypertussia), and cough in response to non-tussive triggers (allotussia).

In these cases, conventional GERD treatments frequently fail, as they do not address the neurobehavioral dimension of the disorder. Here, multimodal interventions—especially the combination of pharmacotherapy, cognitive-behavioral therapy (CBT), and respiratory retraining—have shown increasing clinical value. CBT is particularly effective in modulating the cognitive and emotional frameworks through which patients interpret and react to bodily sensations. It helps reduce symptom preoccupation, catastrophic thinking, and habitual coughing behaviors, thereby restoring cortical inhibition over maladaptive reflex pathways [8,9,10].

For patients with objectively confirmed reflux—typically verified through impedance-pH monitoring or endoscopy—and persistent cough despite maximal medical therapy, surgical options remain a viable consideration. Laparoscopic Nissen fundoplication, which reinforces the lower esophageal sphincter, has been associated with symptom resolution rates between 70% and 85%, particularly in well-selected patients without significant esophageal dysmotility [4,17,27, 28]. However, the invasive nature of the procedure, coupled with risks such as gas bloat syndrome and dysphagia, necessitates rigorous patient selection and careful consideration of cost-effectiveness.

Finally, complementary and integrative approaches—notably herbal treatments—have garnered increasing interest. Randomized trials examining compounds such as Ojeok-San plus Saengmaek-San, rooted in East Asian medical traditions, have shown statistically significant improvements in cough severity, GERD symptoms, and quality of life scores, likely due to their anti-inflammatory and mucosal protective properties [17]. While promising, these findings must be interpreted cautiously, given the limited sample sizes, variable methodological quality, and lack of long-term safety data. Larger-scale, placebo-controlled studies are needed to validate their efficacy and define their role in standard clinical practice.

1. **CONCLUSION**

Chronic cough associated with GERD is a complex and multifactorial condition, often extending beyond acid reflux to involve neurogenic and psychogenic pathways. While PPIs remain the first-line treatment, a significant number of patients benefit more from integrated strategies that include neuromodulators, behavioral therapy, and, in selected cases, surgical intervention. Clinicians should adopt a personalized, multidisciplinary approach when managing refractory chronic cough, taking into account both physiological and psychological contributors to symptom persistence.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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